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Chemotherapy Induces Ovarian Vascular Damage and Hinders Ovarian Function in Mice

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While chemotherapy has improved the survival rate of patients with varying cancers, it has also produced off-target toxicities. A study with premenopausal breast cancer patients reported significantly reduced ovarian blood flow and volume immediately following chemotherapy. This indicates chemotherapy can induce vascular damage and hinder ovarian function. Ovarian vascular damage caused by chemotherapy can contribute to premature ovarian aging and related complications, but ovarian vascular toxicity is understudied. Furthermore, there are currently no treatments that protect the ovary from the gonadotoxic side effects of chemotherapy. The findings from this study will aid in preserving ovarian function from chemotoxicity in female cancer survivors, leading to maintenance of endocrine function and reproductive lifespan. We hypothesize different chemotherapeutic agents variably affect ovarian vasculature and proangiogenic agents might ameliorate vascular toxicity in the ovary caused by chemotherapy. 1-month-old, CD-1 mice were injected intraperitoneally with cisplatin, cyclophosphamide (CPA), or doxorubicin. Ovaries from postnatal day 5, CD-1 mice were cultured with either 4-Hydroperoxy-cyclophosphamide (4-HC) only, 4-HC with vascular endothelial growth factor 165 (VEGF165, proangiogenic), or 4-HC with VEGF165b (antiangiogenic) to examine direct effects of chemotherapy and adjuvants. Ovaries from mice treated with cisplatin (N=9), CPA, or doxorubicin exhibited reduced ovary weight and decreased CD31/PECAM-1 (platelet endothelial adhesion molecule) expression compared to control mice. *Ex-vivo* cultured ovaries with chemotherapy further demonstrated that CD31 expression in the ovarian cortex decreased after chemotherapy treatment, implying diminished blood vessels. VEGF165 treatment appeared beneficial against 4-HC-related vascular toxicity while VEGF165b appeared to have further diminished CD31 expression compared to 4-HC only treatment. We demonstrate different chemotherapies impair ovarian function and affect vascularization within mice ovaries. This indicates the blockage of nutrients and oxygen delivery to growing ovarian follicles halts folliculogenesis within the ovary in addition to depletion of ovarian reserve. VEGF165 plays a beneficial role in ovarian vasculature insult following chemotherapy, suggesting the necessity for the quantification of vascular function parameters using *in vivo* bioimaging and for elucidating mechanisms of ovarian vascular toxicity. Understanding these mechanisms may allow for development of treatments that minimize chemotherapy-induced vascular insult in the ovaries and maintain endocrine homeostasis to improve the quality of life for young female cancer patients.